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אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
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(בעברית) תולדות פיפרידין, הכנתן ותכשירי דוקחות המכילים אותן
(Hebrew)

(באנגלית) Piperidine compounds, their preparation and pharmaceutical compositions containing them
(English)

מבקש בזאת כי ינתן לי עליה פטנט hereby apply for a patent to be granted to me in respect thereof.

• בקשת חלוקה — Application of Division	• בקשת פטנט מוסף — Application for Patent Addition	• דרישה דין קדימה Priority Claim		
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Signature of Applicant

For the Applicants,
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By: —

זיום 9th בחודש April שנת 1989
Thi: of of the year

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89903/2

תרכובות פיפרידין, הכנתן ותכשירי רוקחות המכילים אותן

Piperidine compounds, their preparation and pharmaceutical compositions containing them

NOVO NORDISK A/S

C: 77316

The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in the treatment of anoxia, ischemia, migraine and epilepsy.

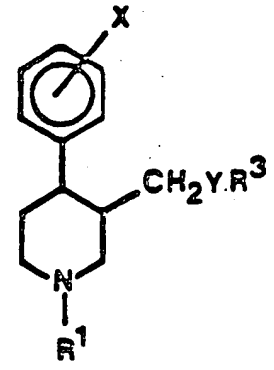
It is well known that accumulation of calcium in the brain cells (calcium overload) is seen after periods of uncontrolled hyperactivity in the brain, such as after convulsions, migraine, anoxia and ischemia. As the concentration of calcium in the cells is of vital importance for the regulation of cell function, an uncontrolled high concentration of the cell calcium will lead to, or indirectly cause the symptoms and possibly also the degenerative changes combined with the above diseases.

Therefore calcium overload blockers selective for brain cells will be useful in the treatment of anoxia, ischemia, migraine and epilepsy.

Well known calcium antagonists such as nifedipine, verapamil and diltiazem have activity against pheripheral calcium uptake, e.g. in blood vessels and the heart, however have shown only very low activity against calcium overload in brain cells.

Accordingly it is an object of the invention to provide novel compounds having activity against calcium overload in brain cells.

The novel compounds of the invention are piperidine compounds having the general formula I



(I)

wherein

R^3 is 3,4–methylenedioxyphenyl, phenyl or naphthyl, optionally substituted with one or more halogen, C_{1-6}–alkoxy, phenoxy, cyano, C_{2-6}–alkenyl, C_{1-6}–alkyl, trifluoromethyl or C_{3-5}–alkylene; and

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R^1 is straight or branched C_{1-4}–alkyl substituted with one or more cyano, C_{1-2}–alkoxycarbonyl, dimethylamino, hydroxy, carbamoyl, methyl–substituted or unsubstituted piperidyl, morpholinyl, thiomorpholinyl, dioxolyl, tetrahydrofuranyl, C_{1-8}–alkoxy or C_{3-8}–cycloalkyl, or R^1 is straight or branched C_{5-8}–alkyl optionally substituted with one or more halogen, cyano, C_{1-2}–alkoxycarbonyl, dimethylamino, hydroxy, carbamoyl, methyl–substituted or unsubstituted piperidyl, morpholinyl, thiomorpholinyl, dioxolyl, tetrahydrofuranyl, C_{1-8}–alkoxy or C_{3-8}–cycloalkyl; and

0.4.89

X is hydrogen, halogen, trifluoromethyl, hydroxy, cyano or C_{1-8}–alkoxy; and

Y is O or S;

provided that R^1 is not unsubstituted C_{5-8}–alkyl, C_{1-8}–alkoxy–C_{1-8}–alkyl or C_{3-8}–cycloalkyl–C_{1-8}–alkyl, when R^3 is 3,4–methylenedioxyphenyl, phenyl or naphthyl optionally substituted with one or more C_{1-6}–alkyl, C_{1-6}–alkoxy or C_{3-5}–alkylene and X is hydrogen or halogen; or a salt thereof with a pharmaceutically acceptable acid.

Preferred compounds of formula I are compounds wherein,

R^3 is 3,4-methylenedioxyphenyl, optionally substituted with halogen or C_{1-6}-alkoxy or phenyl substituted with C_{3-5}-alkylene, and/or R^1 is straight or branched C_{5-8}-alkyl, and/or X is hydrogen, halogen, trifluoromethyl or C_{1-6}-alkoxy.

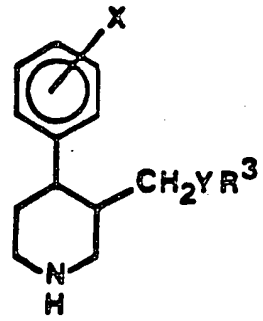
Aryl is intended to mean carboxylic aromatic rings, preferably phenyl.

Heteroaryl is intended to mean mono or fused dicyclic rings of up to 12 carbon atoms including one or more heteroatoms.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts.

The invention also relates to a method of preparing the above mentioned compounds.These methods comprise

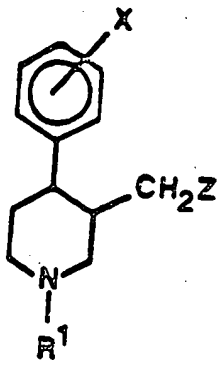
a) reacting a compound having the general formula II



(II)

wherein R^3, X and Y have the meanings defined above, with a compound having the the general formula R^1-Z , wherein Z is a leaving group such as halogen and R^1 has the meaning defined above, or

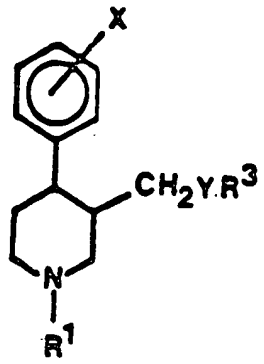
b) reacting a compound having the general formula III



(III)

wherein R^1 and X have the meanings defined above, and Z is a leaving group, with a compound having the the general formula R^3-YH, wherein Y is O or S and R^3 has the meaning defined above, or

c) reacting a compound having the general formula I,



(I)

wherein X, R^1, R^3 and Y have the meanings defined above, with bromine, and optionally thereafter forming a salt with a pharmaceutically acceptable acid.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit calcium uptake into brain synaptosomes.

PRINCIPLE

Depolarization of neuronal membranes leads to an opening of so-called 'voltage operated calcium channels' (VOC) in the membranes which allows a massive influx of calcium from the extracellular space. A crude synaptosomal preparation (so-called P_2 fraction) contains small vesicles surrounded by neuronal membrane and it is possible in such a preparation to study a depolarization-induced opening of VOC. In the present model ^{45}Ca influx is induced in the synaptosomes by depolarization with elevated potassium concentrations, and the effect of test substances on this stimulated uptake is studied (Nachshen, D.A. and Blaustein, M.P., Mol. Pharmcol.,

16, 579 (1979)).

ASSAY

A male Wistar rat is decapitated and the cerebral cortex removed and homogenized in 10 ml of ice-cold 0.32 M sucrose using a glass homogenizer with a teflon pestle. All subsequent steps for isolation of synaptosomes are done at 0-4°C. The homogenate is centrifuged at 1000 x g for 10 min and the resulting supernatant is re-centrifuged at 18000 x g for 20 min. This pellet (P_2) is resuspended in 0.32 M sucrose (5 ml per g of original tissue) with a teflon pestle.

Aliquots (0.050 ml) of this crude synaptosomal suspension are added to glass tubes containing 0.625 ml of NaCl buffer (136 mM NaCl, 4 mM KCl, 0.35 mM $CaCl_2$, 1.2 mM $MgCl_2$, 20 mM Tris HCl, 12 mM glucose, pH 7.4) and 0.025 ml of various drug solutions in 48% Ethanol. The tubes are pre-incubated for 30 min on ice and then for 6 min at 37°C in a water bath.

The uptake is immediately initiated by adding 0.4 ml of $^{45}CaCl_2$ (specific activity = 29-39 Ci/g; 0.5 Ci/assay), in 145 mM NaCl for non-depolarized samples and in 145 mM KCl for depolarized samples. The incubation is continued for 15 s.

The uptake is terminated by rapid filtration through GF-C glass fiber filters which are washed three times with 5 ml of a cold solution containing 145 mM KCl, 7 mM EGTA and 20 mM Tris HCl, pH 7.4. The amount of radioactivity on the filter disc is determined by liquid scintillation spectrometry.

TEST PROCEDURE

Test substances are dissolved in 10 ml of 48% ethanol at a concentration of 0.44 mg/ml. Dilution are made in 48% ethanol. Experiments are performed in quadruplicate. Controls

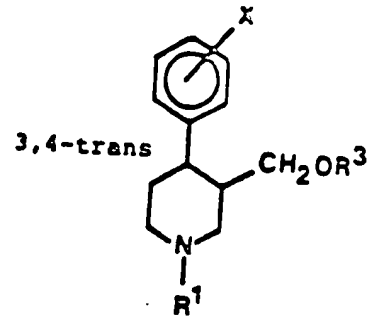
for depolarized and nondepolarized samples are included in the assay and test substances are only tested in depolarized samples.

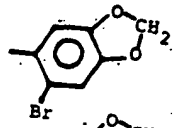
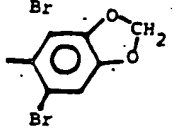
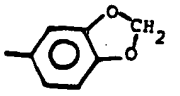
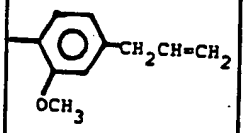
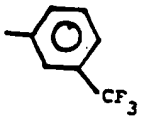
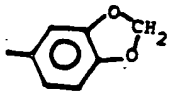
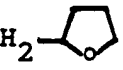
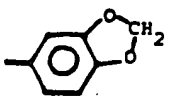
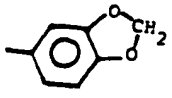
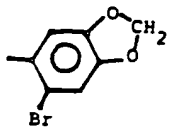
RESULTS

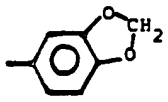
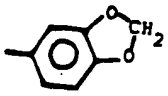
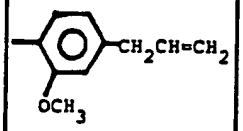
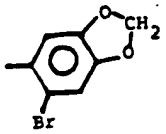
Test values are given as MEC (minimal effective concentration, µg/ml), which inhibit stimulated uptake of ^{45}Ca significant different ($P < 0.05$, Student's t-test) from control.

Test results obtained by testing some compounds of the present invention are given in the following table 1.

TABLE 1



R^1	R^3	X	OPTIC FORM	MEC µg/ml
$-(CH_2)_3CH_3$		4-F	(-)	0.3
$-(CH_2)_4CH_3$		H	(-)	0.3
$-(CH_2)_4CH_3$		4-OCH_3	(+-)	1
$-CH_3$		H	(+-)	1
$(CH_2)_4CH_3$		H	(+-)	1
$-(CH_2)_3-N\langle S$		4-F	(-)	0.3
$-CH_2-$ 		-	(-)	1
$-CH_3$		3-CF_3	(+-)	1
$-(CH_2-)_3-N\langle S$		4-F	(-)	1

$-(CH_2)_4CH_3$		$3-CF_3$	(+-)	0.3
$-(CH_2)_4CH_3$		$4-O(CH_2)_4CH_3$	(+-)	0.3
$-(CH_2)_3CH_3$		H	(+-)	0.3
$-(CH_2)_4CH_3$		4-F	(+)	0.3

* * * * *

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof. In such forms they may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective calcium overload blocking amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, penta-

erythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets,dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir or the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0	mg
Lactosum	67.8	mg Ph.Eur.
Avicel™	31.4	mg
Amberlite™IRP 88	1.0	mg
Magnesii stearas	0.25	mg Ph.Eur.

Due to the high calcium overload blocking activity , the compounds of the invention are extremely useful in the treatment symptoms related to an accumulation of calcium in brain cells of mammals , when administered in an amount effective for blocking calcium overload in brain cells . The important calcium overload blocking activity of compounds of the invention includes both activity against anoxia, ischemia, migraine and epilepsy . The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of a calcium overload blocker , and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective calcium overload blocking amount, and in any event an amount which is effective for the treatment of anoxia, ischemia, migraine or epilepsy, traumatic head injury and neurodegerative diseases due to their calcium overload blocking activity. Suitable dosage ranges are 1-200 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

(-)-trans-1-(2-cyanoethyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride

1 g of (-)-trans-4-(4-fluorophenyl)-3-(3,4-methylene dioxyphenoxymethyl)-piperidine hydrochloride in 50 ml 99.9% ethanol was mixed with 3-bromopropionitrile (7 ml) and 2 g potassium carbonate. The mixture was refluxed for 70 h. After cooling 25 ml acetone and 25 ml diethylether were added, the precipitate filtered off, and the filtrate evaporated in vacuo. The residue was extracted with 1 N NaOH/ether, the ether layer dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in acetone and excess conc. HCl was added. Subsequent evaporation gave a hard glass, which was purified on a silica gel column using 99.5% ethanol as eluent. The title compound was isolated, and its structure confirmed by the IR and NMR data. M.p. 156°C.

The following compounds were prepared in the same manner from (-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride and the relevant halogeno compound (the actual halogen given). Oxalates were prepared from the free base by mixing equimolar amounts of amine and oxalic acid (anhydrous) in acetone solution, which caused precipitation of the oxalate after few min at RT or in the fridge:

(-)-trans-1-(3-(4,4-dimethyl-1-piperidyl)-propyl)-4-(4-fluorophenyl)- 3-(3,4-methylenedioxyphenoxymethyl)-piperidine dihydrochloride, from equimolar amounts of the "piperidine" and the chloro compound. Reflux time 190 h, m.p. 267°C.

(-)-trans-1-(3-dimethylaminopropyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine dihydrochloride, from the chloro compound by reflux for 50 h, a few crystals of iodine added. M.p. 295°C.

(-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-(2-methyl-1-piperidyl)propyl)-piperidine dihydrochloride, from equimolar amounts of "piperidine" and the chloro compound by reflux for 3 h, a few crystals of I_2 added. M.p. 250°C.

(-)-trans-1-(2-ethoxycarbonylethyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine oxalate, from the bromo compound, reflux time 2 h, m.p. 51°C, purified by column chromatography on silicagel using CH_2Cl_2/CH_2OH 9:1 as eluent.

(-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-thiomorpholinylpropyl)-piperidine dihydrochloride, from equimolar amounts of "piperidine" and the chloro compound, a few crystals I_2 added, reflux time 3 h, m.p. 267°C.

(-)-trans-1-carbamoylmethyl-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride, from the iodo compound, reflux for 2 h, m.p. 104°C.

(-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-morpholinopropyl)-piperidine dihydrochloride, from equimolar amounts of "piperidine" and the chloro compound, a few crystals of iodine added, reflux for 30 h, m.p. 108°C.

(-)-trans-1-(4-cyanobutyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound by addition of a few iodine crystals, and reflux for 1 h. The free bases was purified on a silicagel column

using CH_2Cl_2/CH_3OH 9:1 as eluent, m.p. 89°C.

(-)-trans-1-(1,3-dioxolyl-2-methyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound, addition of one iodine crystal, reflux for 120 h, m.p. 53°C.

(-)-trans-4-(4-fluorophenyl)-1-tetrahydrofurfuryl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound, reflux time 7 h, purified on silicagel column, eluent CH_2Cl_2/CH_3OH 9:1, hard glass. Identified by NMR and MS data. MS (m/e, % of base peak): 413,5; 343,38; 342,100; 204,25; 137,28; 109,38; 83,42; 58,100; 57,55.

(-)-trans-4-(4-fluorophenyl)-1-(6-hydroxyhexyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the chloro compound, addition of a few crystals of iodine, reflux for 24 h, purified by column chromatography on silicagel CH_2Cl_2/CH_3OH 9:1 as eluent hard glass. Identified by IR, NMR and MS-data. MS (m/e, % og base peak): 429,3; 343,15; 342,55; 204,10; 171,10; 137,12; 109,15; 58,100.

(-)-trans-4-(4-fluorophenyl)-1-(3-hydroxypropyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound, reflux 7 h, isolated as a hard glass, identified by IR and NMR.

EXAMPLE 2

(+-)-trans-1-methyl-3-(6-bromo-2-naphthoxymethyl)-4-phenyl-piperidine hydrochloride

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6-bromo-2-naphthol (2.45 g) was dissolved in MIBC (40 ml). NaOH (0.52 g) was added, and the mixture was stirred for ½ h. (+-)-trans-1-methyl-4-phenyl-3-phenyl-sulfonyloxymethyl-piperidine (3.5 g) dissolved in MIBC (50 ml) was added to

the "phenolate" solution, heating to 110°C for 6 h. The reaction mixture was evaporated to dryness and the residue extracted with OH/ether. The ether layer was dried (Na_2SO_4) filtered and evaporated to dryness. The crude product was purified on silicagel, petrolether/CH_3OH 1:1 as eluent. The purified product was dissolved in ether and precipitated with excess conc. HCl-solution. Reprecipitation from acetone/-ether gave 0.7 g compound, m.p.225°C.

In the same manner were prepared the following compounds from (+-)-trans-1-methyl-4-phenyl-3-phenylsulfonyloxymethyl-piperidine and the appropriate substituted phenol or naphthol. Oxalates were prepared by mixing equimolar amounts of "piperidine base" and anhydrous oxalic acid in acetone solution.

(+-)-trans-1-methyl-3-(3-trifluoromethylphenoxymethyl-4-phenylpiperidine oxalate. Heating at 130°C until the sulfoester had reacted as seen by TLC. M.p. 92°C.

(+-)-trans-3-(4-chloro-1-naphthoxymethyl)-1-methyl-4-phenyl-piperidine oxalate. Heating to 110°C for 14 h. M.p. 88°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-methyl-4-phenylpiperidine oxalate. Reaction time 40 h at 110°C. M.p. 137°C.

(+-)-trans-1-methyl-3-(3-phenoxyphenoxymethyl)-4-phenylpiperidine oxalate. M.p. 166°C.

(+-)-trans-3-(2-cyanophenoxymethyl)-1-methyl-4-phenylpiperidine oxalate. M.p. 108-110°C.

EXAMPLE 3

(+-)-trans-3-(3-trifluoromethylphenoxymethyl)-4-phenylpiperidine hydrochloride

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was prepared by means of alpha-chloroethyl chloroformate using the method described in J. Org. Chem. 49 (1984) 2081 (R.A. Olofson, J.T. Martz, J.P. Senel, M. Piteau and T. Malfroot). Na-dried toluene was used as solvent instead of 1,2- dichloroethane in the primary reaction. M.p. 171°C.

The following compounds were prepared in exactly the same manner by N-dealkylation of the corresponding N-methyl compound.

(+-)-trans-4-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine. The hydrochloride was extracted with NaOH/ether, the above mentioned compound was precipitated from acetone/ether, m.p. 184°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-4-phenylpiperidine oxalate. The hydrochloride was extracted with OH^-/ether, the ether phase evaporated to dryness, and the residue dissolved in acetone and precipitated with an equimolar amount of anhydrous oxalic acid in acetone solution, m.p. 101°C.

(+-)-trans-3-(3-phenoxyphenoxymethyl)-4-phenylpiperidine oxalate. The hydrochloride was extracted with OH^-/ether, the ether phase evaporated to dryness, and the residue dissolved in acetone and precipitated by means of an equimolar amount of anhydrous oxalic acid in acetone solution. M.p. 138-142°C.

EXAMPLE 4

The following compounds were prepared using the alkylation method described in example 1.

(+-)-trans-3-(3-trifluoromethylphenoxymethyl)-1-pentyl-4-phenylpiperidine oxalate, from (+-)-trans-3-(3-trifluoromethylphenoxymethyl)-4-phenylpiperidine and pentyl bromide by reflux for 10 h. M.p. 130°C.

(+-)-trans-4-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine oxalate, from the corresponding unsubstituted piperidine and 1-bromopentane by reflux for 12 h, m.p. 213°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-pentyl-4-phenylpiperidine oxalate, by reflux of the corresponding unsubstituted piperidine with pentyl bromide for 16 h, m.p. 116°C.

(+-)-trans-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-4-(3-trifluoromethylphenyl)-piperidine hydrochloride from the corresponding unsubstituted piperidine by reflux for 1 h with pentylbromide. M.p. 166.6°C.

(+-)-trans-1-pentyl-3-(3-phenoxyphenoxymethyl)-4-phenylpiperidine oxalate from the corresponding unsubstituted piperidine and pentylbromide by reflux for 2 h. M.p. 77°C.

(+-)-3-(4-allyl-2-methoxyphenoxymethyl)-1-pentyl-4-(3-trifluoromethylphenyl)-piperidine oxalate, prepared from 1-bromopentane and 3-(4-allyl-2-methoxyphenoxymethyl)-4-(3-trifluoromethylphenyl)piperidine by reflux for 10 h. M.p. 130.4°C.

(+-)-3-(4-allyl-2-methoxyphenoxymethyl)-1-pentyl-4-(4-trifluoromethylphenyl)-piperidine oxalate, prepared from the corresponding unsubstituted piperidine as the oxalate and pentylbromide, purified on silicagel column CH_2Cl_2/CH_3OH 9/1 as eluent. M.p. 141.2°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-butyl-4-phenylpiperidine oxalate. Preparation from 1-bromobutane and the unsubstituted piperidine by reflux for 5.5 h. M.p. 74.9°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-cyclopropylmethyl)-4-phenylpiperidine oxalate, from cyclopropylmethylbromide and unsubstituted piperidine by reflux for 2 h. M.p. 80.1°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-4-phenyl-1-propylpiperidine oxalate, from 1-bromopropane and unsubstituted piperidine by reflux for 6 h. M.p. 81°C.

(+-)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-hexyl-4-phenylpiperididne oxalate, from the corresponding unsubstituted piperidine and 1-bromohexane by reflux for 144 h. M.p. 114°C.

EXAMPLE 5

(+-)-trans-4-(4-methoxyphenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine, hydrochloride

(+-)-trans-3-methoxycarbonyl-4-(4-methoxyphenyl)-1-methylpiperidine was prepared from arecoline and 4-bromoanisole as described by Plati et. al. (J. Org. Chem. 22 (1957) 261).

9.6 g of this compound was reduced with $LiAlH_4$ (2.8 g) in dry ether (150 ml), by reflux for 6 h, giving (+-)-trans-3-hydroxymethyl-4-(4-methoxyphenyl)-1-methylpiperidine (6.5 g) as an oil when the normal rinse-up procedure was used.

The crude product was dissolved in toluene (300 ml) triethylamine (7.7 ml) was added, and after stirring for ½ h benzenesulphonyl chloride (4.3 ml) was added, and the mixture stirred at R.T. for 5 h.

The toluene phase was washed with H_2O, dried over $MgSO_4$, filtered and evaporated to dryness resulting in 7.9 g of (+-)-trans-4-(4-methoxyphenyl)-1-methyl-3-phenylsulfonyloxymethyl-piperidine as a yellow oil.

4.1 g of this oil dissolved in MIBC (200 ml) was added to a solution of sesamole (1.7 g) and NaOH (0.5 g) in MIBC (200 ml). The mixture was stirred at reflux temp. for 1.5 h. Subsequently the mixture was extracted with H_2O. The MIBC-phase was isolated and evaporated to dryness.

The resulting mass was extracted from aqueous NaOH/ether, the ether layer was isolated, dried over $MgSO_4$ and evaporated to dryness. The resulting oil was dissolved in acetone and precipitated as its hydrochloride salt by addition of excess conc. HCl-solution.

Yield 1.7 g of (+-)-trans-4-(4-methoxyphenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine, hydrochloride. M.p. 212.2°C. The identity was confirmed by the IR, NMR and MS-data.

(+-)-trans-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-(3-trifluoromethylphenyl)piperidine was prepared using the same reaction sequence starting from arecoline and 1-bromo-3-trifluoromethyl-benzene. M.p. 93.6°C.

EXAMPLE 6

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-butyl-4-(4-fluorophenyl)-piperidine hydrochloride

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(-)-trans-1-butyl-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride (1 g) was dissolved in CH_2Cl_2 (50 ml). Bromine (0.124 ml) was added dropwise at R.T. After stirring for 2 h aqueous NaOH was added, and the

CH_2Cl_2 layer was isolated, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was dissolved in acetone, excess conc. HCl was added, and the above mentioned bromo compound was precipitated by addition of ether. M.p. 116°C.

In exactly the same manner the following compounds were prepared from the corresponding unbrominated compounds.

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-pentyl-4-phenylpiperidine hydrochloride, m.p. 156°C.

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine hydrochloride. M.p. 105°C.

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-(3-dimethylaminopropyl)-4-(4-fluorophenyl)-piperidine dihydrochloride. M.p. 250°C. (d).

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-(2-methoxyethyl)-piperidine hydrochloride. M.p. 65°C (hard glass).

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-cyclopropylmethyl-4-(4-fluorophenyl)-piperidine hydrochloride. M.p. 60°C (hard glass)

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-(2,3-dibromopropyl)-4-(4-fluorophenyl)-piperidine hydrochloride. The crude product was purified on silicagel using CH_2Cl_2/CH_3OH 9/1 as eluent. M.p. 108°C.

(-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-(3-thiomorpholinopropyl)piperidine dihydrochloride. The crude product was purified on silicagel using CH_2Cl_2/CH_3OH 9/1 as eluent. M.p. 241°C.

(+)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine hydrochloride. M.p. 112.3-113.3°C.

EXAMPLE 7

(+-)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-(3-trifluoromethylphenyl)-piperidine

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3-methoxycarbonyl-1-methyl-4-(3-trifluoromethylphenyl)piperidine was prepared as the cis/trans mixture from arecoline and 3-bromo-trifluoromethylbenzene as described (J.Org.Chem. 22 (1957) 261). The product was purified by vacuum distillation. B.p. 90-110°C/0.7 mmHg.

19.2 g of this compound was reduced by means of $LiAlH_4$ (4.85 g) in dry ether (325 ml) in an N_2-atmosphere by reflux for 4 h. After the normal rinse-up procedure followed by purification on a silica gel column using CH_3OH/CH_2Cl_2 (1/1) as eluent 13.2 g oil was isolated. Identified as a cis/trans mixture of 3-hydroxymethyl-1-methyl-4-(3-trifluoromethylphenyl)piperidine by means of ^1H-NMR.

The compound was dissolved in toluene (300 ml), triethylamine (13.5 ml) was added, and the mixture stirred for 1 h. Subsequently benzenesulphonyl chloride (7.5 ml) was added, and the mixture stirred at RT for 70 h. The toluene phase was extracted with H_2O; the separated aqueous layer was extracted with ether and the combined ether and toluene phases were dried with $MgSO_4$, filtered and evaporated to dryness giving 10.3 g of an oil.

5 g of the oil, which was identified as 1-methyl-3-phenylsulphonyloxymethyl-4-(3-trifluoromethyl)piperidine by ^{1}H-NMR, was subsequently dissolved in MIBC (50 ml) and added to a solution of sesamol (1.9) and NaOH (0.5 g) in MIBC (150 ml). The mixture was refluxed for 2 h, stirred at RT overnight and extracted with H_2O. The MIBC-phase was evaporated to dryness, the residue was ecxtracted with NaOH/ether, the ether layer separated acetone and conc. HCl (2 ml) was added resulting in a precipitate.

This was purified on a silica gel column using $CHCl_2/CH_3OH$ 9/1 as solvent, yielding 1.1 g of (+-)-trans-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-(3-trifluoromethylphenyl)piperididne. M.p. 93.5°C

and

0.1 g of (+-)-cis-1-methyl-3-(3,4-methylene dioxyphenoxymethyl-4-(3-trifluoromethylphenyl)piperidine isolated as the oxalate identified by its ^{1}H-NMR and mass spectrum.

(+-)-3-(4-allyl-2-methoxyphenoxymethyl)-1-methyl-4-(3-trifluoromethylphenyl)piperidine oxalate was prepared from 1-methyl-3-phenylsulphonyloxymethyl-4-(3-trifluoromethyl)-piperidine and eugenol as described above by reflux for 1.5 h. M.p. 43.5°C.

EXAMPLE 8

(+-)-trans-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-4-(4-pentyloxyphenyl)piperidine hydrochloride

was prepared by refluxing 4-(4-hydroxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride (0.35 g) with 1-bromopentane (1.8 ml) and K_2CO_3 (1 g) in abs. ethanol (25 ml) for 2 h. The rinse-up procedure described in example 1 gave the title compound. M.p. 148.2°C.

EXAMPLE 9

(+-)-3-(4-allyl-2-methoxyphenoxymethyl)-1-methyl-4-(4-trifluoromethylphenyl)piperidine oxalate

This compound was prepared by exactly the same reaction sequence as described in example 7 using arecolin and 4-bromotrifluorobenzene as the starting materials. The intermediates were identified by means of ^{1}H-NMR and so was the identity of the product confirmed.

EXAMPLE 10

(-)-trans-4-(4-fluorophenyl)-3-(2-iodo-4,5-methylenedioxyphenoxymethyl)-1-pentylpiperidine oxalate

(-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine (1.2 g) was dissolved in CH_2Cl_2 (50 ml). Silver trifluoroacetate (0.66 g) was added, followed by iodine (0.76 g) in CH_2Cl_2 added over a 10 min. period. Stirring for 24 h at R.T. The mixture was filtered, extracted with OH^-, the CH_2Cl_2-phase dried ($NaSO_4$) and subsequently evaporated to dryness. The residue was purified on silica gel and precipitated as the oxalate in acetone solution. M.p. 93.6-94.0°C.

EXAMPLE 11

(+-)-trans-3-(4-propenyl-2-methoxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine oxalate

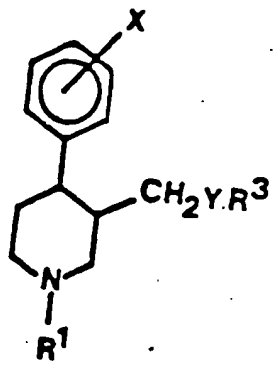
3-chloromethyl-4-(4-fluorophenyl)-1-pentylpiperidine (1 g) dissolved in dry DMF was added to a solution of eugenol (0.6 g) and sodium (0.09 g) in abs. ethanol 50 ml. The

mixture heated to 100°C for 5 days. After 4 days NaH was added.

The reaction mixture was extracted with OH^-/ether, the ethereal layer was dried ($MgSO_4$), evaporated to dryness and purified on a silica gel column using CH_2Cl_2/CH_3OH as eluent. Precipitated as the oxalate from acetone solution. Identified by ^1H and ^{13}C NMR. M.p. 128.0-128.4°C.

CLAIMS

1. A compound of formula I



(I)

wherein

R^3 is 3,4–methylenedioxyphenyl, phenyl or naphthyl, optionally substituted with one or more halogen, C_{1-6}–alkoxy, phenoxy, cyano, C_{2-6}–alkenyl, C_{1-6}–alkyl trifluoromethyl or C_{3-5}–alkylene; and

10.4.89

R^1 is straight or branched C_{1-4}–alkyl substituted with one or more cyano, C_{1-2}–alkoxycarbonyl, dimethylamino, hydroxy, carbamoyl, methyl–substituted or unsubstituted piperidyl, morpholinyl, thiamorpholinyl, dioxolyl, tetrahydrofuranyl, C_{1-8}–alkoxy or C_{3-8}–cycloalkyl, or R^1 is straight or branched C_{5-8}–alkyl optionally substituted with one or more halogen, cyano, C_{1-2}–alkoxycarbonyl, dimethylamino, hydroxy, carbamoyl, methyl–substituted or unsubstituted piperidyl, morpholinyl, thiomorpholinyl, dioxolyl, tetrahydrofuranyl, C_{1-8}–alkoxy or C_{3-8}–cycloalkyl; and

X is hydrogen, halogen, trifluoromethyl, hydroxy, cyano or C_{1-8}–alkoxy; and

Y is O or S;

provided that R^1 is not unsubstituted C_{5-8}–alkyl, C_{1-8}–alkoxy–C_{1-8}–alkyl or C_{3-8}–cycloalkyl–C_{1-8}–alkyl, when R^3 is 3,4–methylenedioxyphenyl, phenyl or naphthyl optionally substituted with one or more C_{1-6}–alkyl, C_{1-6}–alkoxy or C_{3-5}–alkylene and X is hydrogen or halogen; or a salt thereof with a pharmaceutically acceptable acid.

2. A compound of claim 1 wherein R^3 is 3,4-methylenedioxyphenyl, optionally substituted with halogen or C_{1-6}-alkoxy, or phenyl substituted with C_{3-5}-alkylene.

3. A compound of claim 1 wherein R^1 is straight or branched C_{5-8}-alkyl.

4. A compound of claim 1 wherein X is hydrogen, halogen, trifluoromethyl or C_{1-6}-alkoxy.

5. A compound of claim 1 wherein R^3 is 3,4-methylenedioxyphenyl optionally substituted with halogen or C_{1-6}-alkoxy, and R^1 is straight or branched C_{5-8}-alkyl, and X is trifluoromethyl or C_{1-6}-alkoxy.

6. A compound of claim 1 which is (-)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-butyl-4-(4-fluorophenyl)-piperidine hydrochloride.

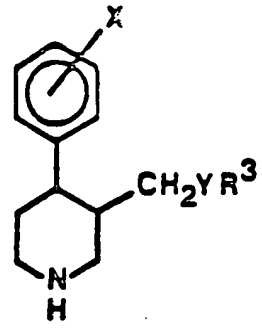
7. A compound of claim 1 which is (-)-trans-4-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-piperidine oxalate.

8. A compound of claim 1 which is (+)-trans-4-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-piperidine oxalate.

9. A compound of claim 1 which is (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-thiamorpholinylpropyl)-piperidine dihydrochloride.

10. A method of preparing a compound according to claim 1, CHARACTERIZED in:

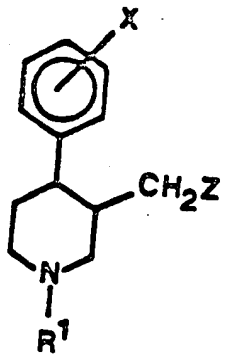
a) reacting a compound having the general formula II



(II)

wherein R^3, X and Y have the meanings defined above, with a compound having the the general formula R^1-Z , wherein Z is a leaving group such as halogen and R^1 has the meaning defined above, or

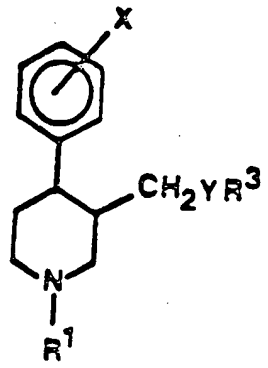
b) reacting a compound having the general formula III



(III)

wherein R^1 and X have the meanings defined above, and Z is a leaving group, with a compound having the the general formula R^3-YH, wherein Y is O or S and R^3 has the meaning defined above, or

c) reacting a compound having the general formula I,



(I)

wherein X, R^1, R^3 and Y have the meanings defined above, with bromine, and optionally thereafter forming a pharmaceutically acceptable salt with an acid.

11. A pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically-acceptable carrier or diluent.

12. A pharmaceutical composition according to claim 11 wherein it is in the form of an oral dosage unit containing 1-100 mg of the active compound.

13. A method of treating an indication related to calcium overload in brain cells of non-human mammals, which comprises the step of administering to the said subject a calcium overload blocking amount of a piperidine compound of claim 1.

14. A method of claim 13 wherein the treatment is directed to the treatment of ischaemia or head injury.

15. A compound of claim 1 which is (+-)-trans-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-4-(3-trifluoromethylphenyl)-piperidine hydrochloride.

16. A compound of claim 1 which is (+)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine hydrochloride.

17. A compound of claim 1 which is (+-)-trans-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-4-(4-pentyloxyphenyl)-piperidine hydrochloride.

18. A compound of claim 1 which is (+-)-trans-3-(4-allyl-2-methoxy-phenoxymethyl)-1-butyl-4-phenylpiperidine oxalate.

19. The use of a compound of claim 1 or a salt thereof with a pharmaceutically acceptable acid, for the preparation of a medicament useful for the treatment of ischaemia or head injury substantially as described in the specification.

For the Applicants,
DR. REINHOLD COHN AND PARTNERS
By: